REMARKS

Claims 1, 2, 4-16 and 31-33 are pending in the instant application. Claims 1, 2, 4-16 and 31-33 have been rejected. Claims 1, 2, 4-16 and 31-33 have been canceled. New claims 34-63 have been added to incorporate the subject matter of the canceled claims. No new matter has been added by these additions to the claims. Reconsideration is respectfully requested in light of these additions and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2, 6-11 and 16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 95/04748 A1), in view of Buchardt et al. (US Patent 6,395,474 B1). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to modify the teachings of Anderson et al. (Peptide nucleic acid oligomers targeting mRNA sequences to control mRNA stability and processing, including those targeted to the 5'CAP, intron/exon junctions, and the 5'-UTR) with the modifications taught by Buchardt et al. (Modifying peptide nucleic acids by attaching ligand to either terminus, including terminal lysine modifications) to design the method of the instant

invention. The Examiner suggests that one would be motivated to modify the oligomers of Anderson et al. with the lysine modifications of Buchardt et al. because the modification is disclosed to strengthen the binding of PNA oligomers to their target nucleic acid. Although the teachings of Anderson et al. do not explicitly teach a method of modulating splicing, absent evidence to the contrary, it would be expected. Applicants respectfully traverse this rejection.

At the outset, Applicants have canceled claims 1, 2, 4-16 and 31-33 and added new claims 34-63. These new claims incorporate the invention of the canceled claims and do not include any new matter. These new claims recite a method of modulating processing of selected wild-type cellular mRNA targets. Support for these new claims can be found throughout the specification as filed.

Anderson et al. disclose methods of modulating viral processes, specifically in cytomegalovirus and papillomavirus. Although this patent discloses peptide nucleic acid oligomers targeting mRNA sequences that control mRNA stability and processing in viral cells, nowhere does this patent teach or suggest a method of modulating processing of wild-type cellular mRNA targets as now claimed. Therefore, this patent fails to teach or suggest the

limitations of the instant invention, which are modulation of processing of wild-type cellular mRNA, not viral mRNA as taught by Anderson et al.

The secondary reference cited by the Examiner fails to overcome the deficiencies in teaching of this primary reference.

Buchardt et al. disclose that binding of peptide nucleic acid oligomers may be modulated through attachment of ligands to the terminus of a peptide nucleic acid. However, nowhere does this patent teach or suggest a method of modulating processing of wild-type cellular mRNA as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims as now amended, which specify methods for modulating processing of wild-type cellular mRNA, are not taught or suggested by the references individually or when combined. Therefore, the limitations of the claims as amended

clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful development of method such as claimed. It is only with the specification in hand that one of skill would understand that the method of the instant invention was a viable method for modulating processing of wild-type cellular mRNA. Further, the cited art fails to provide one of skill with the motivation to design such a method as the prior art cited focuses on viral cell mRNA processing and drugs to treat viral infections. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1, 2, 4-16 and 31-33 have been rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for practice of the claimed method *in vitro* but suggests that *in vivo* practice for therapeutic treatment is not enabled. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that cited references on antisense technology support the position that application of antisense *in vivo* is unpredictable.

The Examiner has pointed to articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Branch (1998) is cited by the Examiner in support of her position. This paper teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense effects. One of skill in the art would not expect to predict the "winning" antisense compound *a*

priori, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.(MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, *i.e.*, the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

The paper of Jen et al. (2000) is cited by the Examiner as discussing the challenges that remain in the use of antisense before it becomes routine. However, again, this paper is not stating that results of well-designed *in vitro* studies would not provide one of

skill in the art with assurance that *in vivo* activity is likely with a compound shown to have activity *in vitro*.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in the instant specification, are directly applicable to predicting *in vivo*

activity. The teachings of the paper by Crooke and the other cited review paper (Branch) provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

However, in an earnest effort to advance the prosecution of this case, Applicants have canceled the pending claims and added new claims that recite *in vitro* applications. Withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **June 25, 2004**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515